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Biophysical Chemistry 110 (2004) 231–238

Biophysical Chemistry

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Control of chemical pattern formation by a clock-and-wavefront type mechanism

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Received 12 February 2004; received in revised form 25 February 2004; accepted 25 February 2004
Available online 27 April 2004

Abstract

The segmentation of many animals ranging from insects to mammals involves the sequential formation of stationary stripes of gene expression that are perpendicular to the growth axis of the developing embryo. This process has been accounted for by a variety of theoretical "clock-and-wavefront" type models that involve the arrest of an oscillation (the clock) at a moving boundary (the wavefront). Here, we demonstrate experimentally that progressive arrest of a homogeneous oscillation can control the symmetry as well as the wavelength of spatial structures in a chemical system. We show how a spontaneously formed, labyrinthine pattern can be converted into a pattern composed of ordered, parallel stripes and confirm a previously predicted proportionality between the wavelength and the period of the homogeneous oscillation. Our experiments provide the first experimental demonstration of a general mechanism for the control of pattern formation that has been hypothesized to operate in the context of biological morphogenesis.

Keywords: Control; Chemical pattern; Clock-and-wavefront

One of the most fundamental questions related to biological morphogenesis is the transformation, or symmetry breaking, of a homogeneous initial state into a state where different regions acquire distinct traits and characteristics. In his seminal paper, Turing [1] considered the problem of symmetry breaking in biological morphogenesis from the perspective of the reaction-diffusion properties of chemical systems. This work revealed that spontaneous symmetry breaking can occur in relatively simple (i.e., in chemical) systems and does not require mechanisms or conditions that are uniquely biological. Since then, reaction-diffusion mechanisms have been applied to numerous biological systems and are now part of major texts in developmental [2] and mathematical [3] biology. In parallel to the studies of reaction-diffusion mechanisms in the context of biological morphogenesis, the past two decades have seen great advances in the area of chemical pattern formation. Patterns generated by reaction-diffusion mechanisms are now observed routinely in the chlorine-iodine-

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doi:10.1016/j.bpc.2004.02.006

malonic acid (CIMA) reaction medium [4–6] and in several other systems (see, e.g., Refs. [7,8]).

During early development, it is often observed that space-period structures are formed at or near a growth zone that is located at the extremity of an elongating organism or tissue. This axial growth typically arises due to a continuously dividing cell population present within the terminal growth zone. Examples include the formation of stationary stripes of gene expression in a number of developing animals, including vertebrate embryos [9–16]. In the chick, cells from the primitive streak are continuously added to the posterior (tail-most) boundary of the presomitic mesoderm (PSM), which grows at a steady rate in the posterior direction [17]. Segmentation occurs at the anterior (head-most) PSM boundary by the clustering of cells from the PSM into structures, the somites, that are repeated along the growth axis. The somites are formed at regular intervals in such a way that the overall length of the PSM remains fairly constant. The continuous addition of cells posteriorly and removal of cells anteriorly makes it appear as if the PSM moves through the developing embryo at a steady velocity.

It has been pointed out by several authors [18–23] that the relative motion between a terminal growth zone, for instance the posterior PSM boundary in the chick, and the daughter cells that are continuously shed from it, may have important implications for biological morphogenesis. If the cell population within the terminal growth zone expresses a morphogen in an oscillatory and synchronous fashion, the movement of the growth zone boundary relative to the shed daughter cells can, at least theoretically, lead to the formation of a stationary space-periodic structure. This would require that the oscillation is arrested either abruptly at the moment the cells traverse the growth zone boundary or gradually as the cells move farther away from it. In other words, a space-periodic structure could be formed when a moving boundary (the wavefront) causes or initiates the arrest of an oscillation (the segmental clock) that is synchronized in the region ahead of it (Fig. 1A and B).

We have previously investigated theoretically how the arrest of an oscillation at a moving boundary can control the appearance and the wavelength patterns in simplified models of reaction-diffusion systems [23,24]. In this paper, we present an experimental validation of this basic mechanism of pattern formation in a chemical system. In the experiments, we exploited the light-sensitivity of the chlorine-dioxide-iodine-malonic acid (CDIMA) reaction medium [25–30] to control both a synchronous oscillation and a boundary where this oscillation is arrested (Fig. 1C). The oscillation was generated by periodically modulating the illumination intensity and the moving boundary was formed by slowly moving a mask that blocks the incident light across the medium. This causes a time-varying chemical composition of the reaction medium in the illuminated region and the arrest of this oscillation as the illumination boundary progresses across the system.

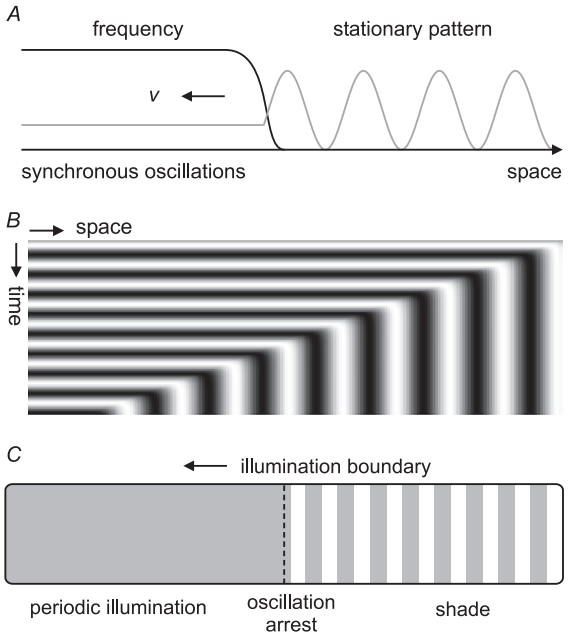

Fig. 1. (A, B) Conversion of a homogeneous oscillation into a stationary pattern by progressive oscillation arrest. (A) A moving boundary (velocity v) establishes a frequency gradient and causes the oscillation to arrest in different phases at different spatial locations. (B) Space–time plot illustrating the conversion of the oscillation into a stationary pattern. One 'segment' is established for each oscillation completed. (C) Experimental implementation in the light-sensitive CDIMA reaction system. Periodic illumination drives a homogeneous oscillation in the concentration of chemical species in the illuminated section of the reactor. Progressive arrest of the oscillation is due to a mask that shields the reactor from the illumination. The mask is moved across the reactor (to the left), thereby arresting the concentration oscillation and converting it into a pattern composed of stationary, parallel stripes. Shading denotes high concentrations of a chemical species.

While our experimental system differs in a number of important ways from the biological systems where clock-and-wavefront type mechanisms have been proposed to operate, there are a number of analogies between them. For example, the CDIMA reaction medium spontaneously develops a spatial labyrinthine pattern in the absence of external control. An example of such a pattern is shown in Fig. 2. In this respect, the chemical system is analogous to the cells in the presomitic mesoderm of the chick, which are able to self-organize into somite-like clusters, apparently without the involvement of a segmental clock oscillation [31]. Our experiments demonstrate that oscillation arrest at a moving boundary can control pattern formation, in our case by converting the spontaneously formed labyrinthine pattern into one comprised of parallel stripes, even when the system has an inherent tendency to self-organize. While our observations do not provide evidence for or against the operation of clock-and-wavefront mechanisms in biology, they do demonstrate the correctness of the hypothesis that such mechanisms can control pattern formation in a real system. Moreover, we confirm an earlier prediction [21] that the wavelength of the stripe-pattern generated by progressive oscillation arrest scales linearly with the oscillation period and the velocity of the moving boundary, in a manner that is consistent with the wavelength of the gene expression stripes observed in the developing chick embryo.

Fig. 2. Example of a labyrinthine Turing structure that develops spontaneously in the light-sensitive CDIMA reaction medium in the absence of illumination. The formation of this structure can be completely suppressed by constant or periodic illumination of the medium at sufficiently high intensity.

1. Experimental setup

The experiments were carried out in a thermostatted one-feeding-chamber continuously feed unstirred reactor maintained at 4.0±0.5 °C using an experimental setup described in detail elsewhere [29]. Structures appeared in a circular agarose gel layer (2% agarose, thickness 0.3 mm, diameter 20 mm). The gel layer was separated from the feeding chamber (residence time 4.2 min) by an Anapore membrane (Whatman, pore size 0.2 mm, impregnated with 0.5% agarose gel) and a nitrocellulose membrane (Schleicher & Schnell, pore size 0.45 mm). Reagents of the CDIMA reaction were continuously pumped into the reactor with the following feed-stream concentrations; 0.45 mM I_2, 0.108 mM ClO_2, 10 mM H_2SO_4, 1.2 mM $CH_2(COOH)_2$ and 10 g/l PVA. With these input concentrations, the system spontaneously develops labyrinthine patterns with a wavelength of λ_0=0.53±0.02 mm in the absence of illumination. Illumination was provided by a 300-W halogen lamp. Constant or periodic (square wave) variation in intensity completely suppressed the formation of Turing structures in the illuminated part of the reactor (not shown). Digital images were taken periodically (at 8–9-min intervals) using a charged-coupled device camera.

Mathematical and numerical analysis [23,24] has predicted that stripe formation can be controlled by progressive oscillation arrest in a chemical system capable of forming Turing patterns only when the velocity of the moving boundary exceeds a critical value. This is due to diffusion of chemical species within the medium, which causes the Turing pattern to spontaneously spread spatially. To avoid interference between a spatially spreading Turing pattern and the pattern imposed by progressive oscillation arrest, the boundary has to move at a velocity that exceeds the velocity with which the Turing pattern spontaneously spreads spatially [24]. To ensure the appropriate operating conditions, we estimated the velocity at which spontaneously formed, labyrinthine pattern spreads in the absence of illumination (0.018±0.005

mm/min) and chose a boundary velocity that significantly exceeds this value (v=0.071±0.004 mm/min).

2. Results

In Fig. 3, we compare the pattern observed when progressive oscillation arrest is imposed onto the system with that observed when the oscillation ahead of the moving boundary is absent. The figure shows snapshots of the reactor for periodic illumination (Fig. 3A and B) and for constant illumination (Fig. 3C and D) taken approximately 40 min apart. The position of the boundary, which moves from right to left, is indicated by a vertical arrow in Fig. 3A and C. In Fig. 3B and D, the boundary has moved outside of the displayed region. For periodic illumination, the pattern that emerges in the non-illuminated domain is composed of stripes that are parallel to the moving boundary. The stripe pattern is seen to have some defects. The defects are likely due to a combination of inhomogeneities, such as dust particles and gel density variations, and the intrinsic dynamics of the medium (discussed below).

The stripes observed in Fig. 3A and B are in sharp contrast to the patterns observed in Fig. 3C and D where the illumination is constant, but all other parameters kept unchanged. In the absence of oscillations in the illuminated domain, the pattern that develops in the non-illuminated domain is highly irregular and it is formed at various angles relative to the moving boundary. Direct comparison of Fig. 3A and B with Fig. 3C and D thus indicates that the combination of the homogeneous oscillation and the movement of the illumination boundary, i.e., progressive oscillation arrest, is required for the formation of stripes that are parallel to the moving boundary. Interestingly, while the irregular pattern in Fig. 3C and D does have labyrinthine-like character, it is composed mostly of stripes that are more or less perpendicular to the moving boundary. A similar preference is observed for periodic illumination when the oscillation period is short (see Fig. 4C below). The reason for these observations remains unclear.

We have previously predicted [21,23] that the wavelength λ of the pattern imposed by the progressive arrest of a homogeneous oscillation should be given by the relation ship $\lambda=vT$ where v is the velocity of the moving boundary and T is the period of the homogeneous oscillation ahead of it. To test this prediction, we performed a series of experiments in which the illumination period T was varied, keeping the velocity of the boundary fixed. Fig. 4 shows the correlation between the experimentally observed wavelength, measured from the faint prepattern that appears immediately behind the illumination boundary, and the illumination period. The dashed line shows the theoretically predicted wavelength. The theory is in excellent agreement with the experimental observations. This confirms that the wavelength and

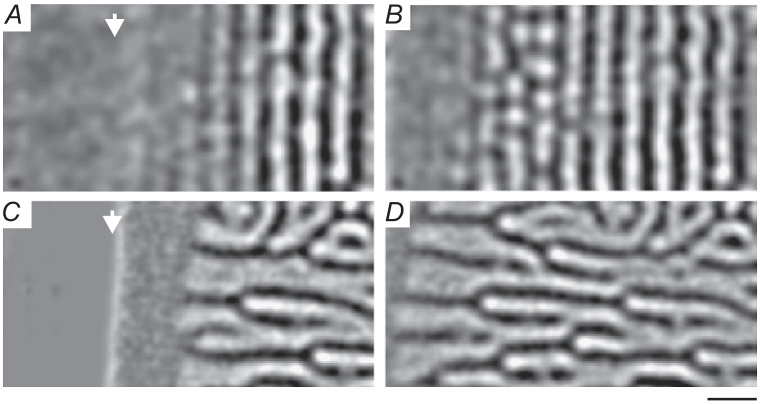

Fig. 3. Control of Turing patterns by progressive oscillation arrest. Each panel shows a 7.5×3.75-mm region of the reactor. The illumination boundary (indicated by arrow) moves from right to left. (A, B) Stripes are formed parallel to the moving boundary when the illumination is periodic (8 min). The snapshots were taken 39 min apart. (C, D) An irregular Turing structure is formed when the illumination is constant. The snapshots were taken 40 min apart. The bar corresponds to 1 mm.

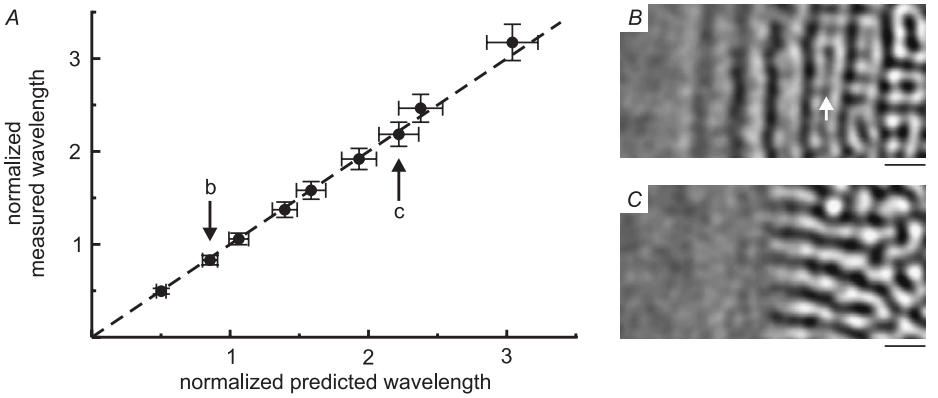

Fig. 4. (A) Correlation between the prepattern wavelength λ (circles), measured from the parallel stripes formed immediately behind the moving boundary, and the theoretically predicted wavelength $\lambda=vT$ (dashed line), both normalized by the wavelength λ_0 of the labyrinthine structure formed in the absence of illumination (λ_0=0.53 mm). The arrows marked 'b' and 'c' give the wavelength of the stripe immediately behind the illumination boundary in panels (B) and (C), respectively. (B) Wave splitting (indicated by the arrow) occurs when the imposed wavelength is too long. (C) An irregular pattern is formed when the wavelength is too short. The bar corresponds to 1 mm.

the symmetry of the patterns observed in the non-illuminated region of the reactor in Fig. 3A and B are indeed controlled by the progressive arrest of the homogeneous oscillation in the illuminated region of the reactor.

A prepattern comprised of parallel stripes is imposed onto the non-illuminated domain for all illumination periods tested. However, the observation of this prepattern does not imply that it is stable or that the pattern that is formed at a distance from the boundary preserves the wavelength and symmetry of the prepattern. In some cases (see, e.g., Fig. 4C) the prepattern cannot be seen by visual inspection and its presence can only be detected by filtering and Fourier analysis. This is due to the internal dynamics of the reaction medium, which allows only patterns with wavelengths in a fairly narrow range to be selected for amplification. The wavelength of the imposed prepattern must lie within this range in order for it to be maintained farther away from the boundary (see Refs. [23,24] for a detailed discussion).

There are several mechanisms by which the internal dynamics of the medium can respond when the wavelength of imposed prepattern is outside of the range where stable stribes can be maintained. For example, when the imposed pattern has a wavelength that is too long, the internal dynamics of the medium may split the stripes and yield a structure with a wavelength that is decreased by a factor of 2. An example of this is shown in Fig. 4B. For even longer wavelengths, each imposed stripe was observed to split into three parallel stripes (not shown). On the other hand, when the wavelength of the imposed pattern is too short, an irregular labyrinthine-like structure is selected. An example of this is shown in Fig. 4C where the imposed prepattern is too faint to be seen with the naked eye. Similar observations have been made when the stripe patterns were imposed using a striped stationary mask [29,30]. The transient behavior observed while the medium responds to an imposed prepattern could provide insight into the internal dynamics of the medium. Such an analysis is, however, beyond the scope of the present investigation.

3. Discussion

We have demonstrated the control of pattern formation by a mechanism that relies on the arrest of a homogeneous oscillation at a moving boundary to establish a space-periodic 'prepattern' composed of parallel stripes. When the wavelength of the imposed prepattern is within the appropriate range, it is amplified and maintained by a combination of reaction and diffusion within the medium. The result is a stable pattern of stationary parallel stripes with a wavelength that depends on the period of the oscillation and on

the velocity of the moving boundary where the oscillation is arrested. Our observations constitute an experimental validation of earlier theoretical predictions regarding the control of pattern formation in Turing-unstable, bistable and oscillatory active media [21,23] and in the Turing-unstable light-sensitive CDIMA reaction system [24]. These theoretical investigations were in turn motivated by morphogenesis in developing embryos.

A theme frequently observed during the development of diverse animals is the sequential formation of segments along the growth axis of the developing embryo. Over the years, sequential segmentation has been explained by a variety of theoretical models [18–23,32–35]. These models are different in their specific details, but they all involve the conversion of an oscillatory process into a stationary pattern by the arrest of the oscillation in different phases at different spatial locations. The main difference between the various models lies in the process that causes the oscillation arrest and whether the arrest occurs abruptly or gradually. For example, Newman [19] proposed a model in which the asymmetric division of a synchronously oscillating cell population within a terminal growth zone gives rise to sequentially formed segments as the oscillation is halted in the shed daughter cells. A related ''clock-and-trail'' model was proposed by Kerszberg and Wolpert [20]. In this model, a ''snapshot'' of the phase of the segmental clock oscillation is preserved in cells at the moment they cross the boundary between the growth zone and the elongating tissue. The mechanism of pattern formation control in our chemical system closely mimics the mechanism that leads to space-periodic structures in these two models.

Experimental evidence that strongly supports the hypothesis that oscillation arrest is involved in the sequential formation of segments has been obtained from the process of somite formation in vertebrates. Gene expression waves observed during somitogenesis in a variety of vertebrate species [9–16] are consistent with the currently popular ''clock-and-wavefront'' (CW) model by Lewis [33]. This model was adapted from an earlier and slightly different CW model by Cooke and Zeeman [32] to explain gene expression patterns observed in the chick. In the CW model by Lewis, a pattern of stationary, parallel gene expression stripes arises from the gradual arrest of a homogeneous segmental clock oscillation. This arrest is induced by the passage of a 'maturation' wavefront. The model assumes that the wavefront arises from a gradient in chronological cell age, which, in turn, is established by the temporal order in which the cells were added to the PSM at its posterior boundary. This wavefront has later been identified as a gradient in fibroblast growth factor [36,37], which may allow cells to measure the amount of time they have spent in the PSM [35,38]. While the CW model by Lewis involves a gradual slowing down of the oscillation, it has been shown theoretically [21,23] that the rate at which the oscillation slows down does not influence the pattern that emerges once the oscillation is arrested. In other words, the wavelength and the symmetry of the final pattern are the same for gradual and for abrupt oscillation arrest. Hence, the CW model hypothesized by Lewis (and related models Refs. [21–23,34]) may be considered as variants of the model suggested by Newmann [19] and later by Kerzberg and Wolpert [20] where oscillation arrest is abrupt and whose operation we have here demonstrated in a chemical system.

There are of course many differences between our experiments and the biological systems in which morphogenesis by the progressive arrest of an oscillation has been proposed as a plausible mechanism. For instance, in our experiments, the oscillation and the moving boundary where the oscillation is arrested are controlled externally. These parameters are controlled autonomously in the biological systems by mechanisms that remain to be determined. We did attempt to employ the oscillating capabilities of the CDIMA system as an intrinsically controlled oscillator. These experiments are quite challenging and have so far been unsuccessful. Moreover, our experiments rely on the ability of the CDIMA system to amplify and maintain the imposed pattern as a Turing structure. The formation of Turing structures usually requires fine-tuned parameters and the Turing instability supports only a limited range of wavelengths. For this reason, we believe it to be unlikely that a Turing instability underlies biological segmentation. Systems that are capable of maintaining stationary phase-gradients for an extended period of time and systems capable of forming stable interfaces separating bistable states

are much more robust [23] and are, in our opinion, more likely to be biologically relevant.

Despite the differences between the chemical and the biological systems, there are a number of interesting analogies. As mentioned in the introduction, the CDIMA reaction system and the cells of the chick PSM are both able to self-organize and our experiments demonstrate that progressive oscillation arrest can be used to replace intrinsically selected wavelengths and symmetries with ones that are determined by the oscillation period and the velocity of the wavefront that causes (or induces) its arrest. Moreover, the relationship $\lambda=vT$ between the wavelength of the parallel stripes, the velocity of the wavefront of oscillation arrest v and the oscillation period T ahead of it (Fig. 4A) is in agreement with observations in the developing chick embryo [21]. The wavelength of the stationary gene expression pattern established at the anterior PSM boundary coincides with the length l of individual segments (the somites) and the period T of the segmental clock oscillation in the posterior PSM, and in the primitive streak that feeds cells to the PSM [39], coincides with the periodicity at which somites are formed at the anterior PSM boundary (90 min). Since the PSM grows at its posterior boundary at a rate that corresponds to one somite length for each somite formed, the velocity at which the oscillation arrest progresses through the embryo is given by $\lambda=l/T$. The prediction is then that the wavelength of the stripes should be one somite length (since $\lambda=vT=l$ when $v=l/T$). This is exactly what is observed [9]. As we have pointed out previously [21], the dependence of the wavelength on the posterior growth rate and on the period of the segmental clock may explain why somites tend to become smaller toward the end of somitogenesis where the rate of posterior growth is reduced. It may also explain why embryos that are reduced in size produce the same number of proportionally smaller somites, provided that the smaller embryos have a smaller population of dividing cells and, consequently, a proportionally reduced rate of axial elongation.

Acknowledgements

Experiments were carried out by D.G.M. and A.P.M. with funding from the Spanish MCYT (grant no. BFM2000-0348). M.K. received funding from NSERC, the Danish Research Agency and NIH. M.M. received funding from NSERC.

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